REMARKS

I. Status of Claims

Claims 45-65, 78-109 and 145 are currently pending and stand rejected under 35 U.S.C. §112 first and second paragraphs, U.S.C. §102(e) and under 35 U.S.C. §103(a). Applicants respectfully traverse the rejections and request reconsideration of the application in light of the comments and amendments presented herein.

II. Formalities

As requested by the Examiner, the specification has been amended so that the description of the renumbered Figures correspond to the renumbered Figures.

The specification has also been amended to delete the blank space on page 111.

III. Rejections under 35 U.S.C. §112, first paragraph should be withdrawn.

The Examiner rejected claims 45-65 and 78-109 and 145 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors had possession of the claimed invention. Applicants respectfully traverse the rejection.

Briefly, the claims of the present invention are exemplified by claim 145 which recites that:

> "A method of producing a specific binding pair member, which method comprises: expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides, which library of nucleic acid sequences is provided by mutating nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, wherein said enzyme or fragment thereof is a non-immunoglobulin protein, which enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,
>
> wherein said polypeptides encoded by the library are displayed at the surface of filamentous bacteriophage particles, and wherein genetic material of each

filamentous bacteriophage particle displaying a polypeptide includes nucleic acid encoding the polypeptide displayed on that particle."

At page 3, of the official action, the Examiner notes that the specification does indeed disclose and reports experimental results showing phage display of at least two enzymes, but then proceeds to declare that there is insufficient written description support for the claimed invention stating that:

> "specification disclosure clearly does [sic] not provide an adequate representation regarding the open ended claimed method of producing all known enzymes. However, the instant claims are directed to phage display library of all the known enzymes [sic]. None of which meet the written description of 35 U.S.C. 112, first paragraph."

Applicants respectfully traverse. The Examiner is misapplying the law and is ignoring the plain teachings of the instant specification.

The Examiner correctly identified various portions of the specification which describe the phage display of enzymes or enzyme fragments, for example the Examiner is referred to Example 11 (page 113-115 of substitute specification), Example 12, (page 115-117 of substitute specification. Additionally, the Examiner is referred to page 13, lines 4 to 11 which state that:

> "...the applicants have been able to ***construct a bacteriophage that expresses and displays at its surface a large biologically functional binding molecule*** (*eg* antibody fragments, and ***enzymes*** and receptors) and which remains intact and infectious. The applicants have called the structure which comprises a virus particle and a binding molecule displayed at the viral surface a 'package'..." [***emphasis added***]

Additionally, Applicants urge that the Examiner carefully review the specification at page 22, lines 3 to 14 where it is specifically stated that:

"Another possibility, is the ***display of an enzyme molecule or active site of an enzyme molecule on the surface of a phage*** (see examples 11,12,30,31,32 and 36). Once the phage enzyme is expressed, it can be selected by affinity chromatography, for instance on columns derivatized with transition state analogues. If an enzyme with a different or modified specificity is desired, it may be possible to mutate an enzyme displayed as a fusion on bacteriophage and then select on a column derivatised with an analogue selected to have a higher affinity for an enzyme with the desired modified specificity."

In the face of this explicit disclosure, Applicants contend that the Examiner simply has failed to meet the burden of presenting evidence or reasons why a person of skill in the art would not recognize in the above passages as well as in Examples 11,12,30,31,32 and 36 a description of the invention defined by the claims. Those of skill in the art are well aware of methods of mutating a nucleic acid sequence using standard techniques.

The applicants have also devised a series of novel selection techniques that are practicable only because of the unique properties of rgdps and which readily permit the identification and isolation of rgdps and the nucleic acid encoded therein. The general outline of some screening procedures is illustrated in figure 2 using pAbs as an example type of rgdp.

The population/library of pAbs to be screened could be generated from immunised or other animals; or be created in vitro by mutagenising pre-existing phage antibodies (using techniques well-known in the art such as oligonucleotide directed mutagenesis (Sambrook, J., et al., 1989 Molecular Cloning a Laboratory Manual, Cold Spring Harbor Laboratory Press). This population can be screened in one or more of the formats described below with reference to figure 2, to derive those individual pAbs whose antigen binding properties are different from sample c.."

These techniques are equally applicable to both antibody molecules any other displayed binding pair members as defined in the present specification including non-immunoglobulin proteins such as enzymes.

The Examiner' suggestion that Applicants have not met the written description requirements of 35 U.S.C. §112, first paragraph because they have not listed "all known enzymes" is not only onerous but fails to understand the subject matter of the present invention. As the Examiner correctly pointed out, "...the invention is, for the purposes of the 'written description' inquiry, *whatever is now claimed.*" (Office Action at p.4 *emphasis in original.*) The instant invention, for the first time provides a ***method*** of producing specific binding pair member (*i.e.* in this instance an enzyme or a fragment thereof), by expressing in recombinant host cells a library of nucleic acid sequences that encode a genetically diverse population of enzymes or fragments which enzymes or fragments thereof are able to bind a ligand (in a functional form) and are at least 100 amino acids in length and which are non-immunoglobulin proteins, and displaying the polypeptides on the surface of the filamentous bacteriophage particles. The genetically diverse polypeptides maybe produced from the library of nucleic acid sequences by mutating a nucleic acid that encodes an enzyme or fragment thereof.

It is evident that the initial claims under examination are not directed to a genus of enzymes but to methods of producing enzymes. Hence, the Examiner's protestations that the that only two examples of enzymes are given are inappropriate for rejecting ***method*** claims. The essential goal of the written description requirement is to clearly convey the information that an applicant has invented the subject matter ***which is claimed***. Logic dictates that the focus of this inquiry differs depending on what subject matter is being claimed. The decision in the *Fiddes* case quoted by the Examiner concerned an adequate written description of a DNA invention, *i.e.*, an invention of a chemical DNA compound and not methods. Indeed, the Examiner correctly points out that the claims in *Fiddes* were directed to FGF's and were found unpatentable due to lack of written description for that broad class because the specification only provided the bovine ***sequence*** (Office Action page 4). However, the Applicants submit that case law directed to the written description of novel compositions is not applicable in the instant invention which is directed to novel, non-obvious methods.

It is inappropriate to judge the written description of the presently claimed methods based on a legal standard directed to compositions comprising protein or DNA. The fundamental consideration of describing what an applicant has invented is different in the context of a method of

producing an enzyme or a fragment thereof invention as discussed *supra*. As stated in the new written description guidelines, "The description need only describe in detail that which is new or not conventional." (See 66 FR 1106).

The present application does not attempt to claim a genus of compounds that must be structurally distinguished from all other compounds. Instead, the present invention is directed to ***a method of producing*** an enzyme or a fragment thereof, and is based in part on the discovery that using the methods of the present invention, it is now possible to display enzymes (non-immunoglobulin proteins) of at least 100 amino acids in length, and optionally at least 200 amino acid (claim 45), on the surface of the filamentous bacteriophage particles. Thus, the methods of the instant invention represent a novel and nonobvious way to produce enzymes and other polypeptides, it is not specifically directed to the two proteins that the Examiner discusses in the official action. The Written Description Guidelines recognize that an Applicant can show possession of the claimed invention by describing distinguishing, identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention, (see, 66 FR 1104, col. 3.) or by describing the... acts of a process (see 66 FR 1106, end of first to beginning of second column). "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognized that the inventor had possession of the claimed invention." (66FR 1105, col. 3.)

In the case of the presently claimed method, the distinguishing characteristic need not be structural characteristics of compounds, but rather can be steps in a method of producing enzymes using display of an enzyme molecule or active fragment of an enzyme molecule on the surface of a phage where the enzyme molecule is at least 100 amino acids in length. (See 66 FR 1106, cols. 1-2, distinguishing structures of products from acts of a process.) Since the present invention is directed to such methods and because the Applicants describe each step of the process, Applicants submit that claim 145 reasonably conveys the invention to persons of ordinary skill and is reasonably commensurate in scope with the teachings of the invention and is in full compliance with "The Written Description Guidelines". These claims will not "encompass" compounds, but rather describe *a particular production method for obtaining enzymes*, and this use represents one of the Applicant's contributions to this field.

Given the teaching of the present invention, one of skill in the art will be able to produce an enzyme that is able to bind a ligand, has an amino acid sequence of about 100 amino acids and for which the parent nucleic acid sequence is known. A person reading the specification in its entirety would understand that the instant inventors invented and fully described the necessary steps for performing the method in which an enzyme of about 100 amino acids may be produced and displayed on a bacteriophage particle which contains nucleic acid encoding the enzyme. Thus, contrary to the Examiner's suggestion, the instant case is not limited to producing an alkaline phosphatase or a staphylococcal nuclease but may be used to produce any enzyme.

It is also worth noting that alkaline phosphatase and stahpylococcal nuclease are not related enzymes. Indeed, as explained in the examples, alkaline phosphatase is only active enzymatically as a dimer. The experiments show that the enzyme activity is obtained when alkaline phosphatase is displayed on the surface, indicating that proper dimerisation ("functional form") is taking place. The experimental demonstration of success with two such very different enzymes, exemplifies and emphasizes the breadth of application of the invention, and clearly reflects that the invention as defined by the claims was in the possession of the inventors at the time of filing.

In light of the explicit teachings of the present invention, Applicants submit that the claims are in full compliance with "The Written Description Requirements" of 35 U.S.C. §112 first paragraph and therefore that the rejections should be withdrawn.

IV. Rejections under 35 U.S.C. §112, second paragraph should be withdrawn.

The Examiner rejected all the claims under 35 U.S.C. §112, second paragraph for various reasons. Applicants respectfully traverse the rejections for the reasons provided below. In light of this response, Applicants submit that the claims are now in condition for allowance and request a speedy indication of such a favorable disposition.

Claims 45-47, 78-85 and 145 were rejected under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps. The Examiner states that "...[t]he omitted steps are: how to produce a member of a specific binding pair...." Applicants strongly disagree with the Examiner and have discussed this rejection with the Examiner on a number of occasions.

The independent claims are directed to a "method of producing a member of a specific binding pair..." In essence, the point is that specific binding pair members are produced on the surface of filamentous bacteriophage particles by expressing encoding nucleic acid in recombinant cells. It is ***not*** a requirement for ***production*** of a specific binding pair member that the specific binding pair member be selected, screened, isolated or the subject of any other process step. The steps recited in, for example, claim 145, are all the steps that are required for the specific binding pair member to be produced and indeed displayed at the surface of filamentous bacteriophage particle. The Examiner's requirement for a screening, or selection step is onerous and overly limiting of the scope of the claimed invention. The independent claims recite all the steps necessary for the "production" of the specific binding pair member and the additional steps of affinity selection in the presence of a ligand are not needed in the independent claim and are presented in dependent claims. Applicants representative discussed this exact rejection with the Examiner in relation to U.S. Serial No 09/196,522 on February 14, 2001 and February 15 2001 and again on March 15, 2001 with Examiner Ponnaluri and Examiner Celsa pointing out the above discussions and the Examiners agreed that the claims reciting the term "producing" the claims are ***not*** omitting an essential step and it was agreed that this rejection would be withdrawn. Applicants request that in light of these comments and discussions, the Examiner should formally withdraw this rejection as she indicated in her telephone conference with the Applicants' representative.

Claim 48 was rejected as allegedly being indefinite by reciting "...a mixed population of displayed specific..." it is the Examiner's position that it is not clear what the applicant means by mixed population of displayed polypeptide, the examiner is confused because "claim 145 recites that at the surface of the phage the polypeptide is displayed". The Examiner requested further clarification. In the previous response, Applicants stated that " it is the specific binding pair member that is associated in its respective particle with encoding nucleic acid and that "mixed population of polypeptides" refers to a population of different polypeptides." (See page 19 of Applicants' response filed October 5, 2000). The Examiner has not responded to Applicants response and has provided no indication of why in view of that response the term "mixed population of polypeptides" is unclear. Applicants believe that in light of their previous response the term "mixed population of displayed specific binding pair members" is clear. Applicants request that if the Examiner insists on

maintaining a lack of clarity rejection, the Examiner elaborate as to why this term is deemed to be not clear as it is not apparent that Applicants prior response to the same rejection was considered.

Claims 55, 57 and 94-101 were rejected as being vague for reciting in step (ii), producing from nucleic acid obtained in step (I) nucleic acid which encodes a specific binding pair member. In response to the Examiner's requested additional clarification of this term, Applicants maintain that step (ii) is not vague and that one of skill in the art would recognize that step (ii) simply means that the nucleic acid of step (i) is used to make additional nucleic acid. Methods for making such additional nucleic acid are well known to those of skill in the art and also are disclosed in the specification and are well known to those of ordinary skill in the art, e.g. PCR. Applicants have previously addressed, and the Examiner has previously withdrawn a similar rejection that was advanced in related case 09/197,224 (see Official Action dated March 28, 2000 and response thereto dated September 28, 2000). If the Examiner requires further specific discussions regarding this feature she is invited to contact the undersigned representative.

Claims 60-65 and 102-109 were objected to as allegedly being vague and indefinite for reciting "...nucleic acid which encodes a derivative specific binding pair member..." The Examiner states that it is not clear whether the derivative has similar properties as the specific binding pair member and or whether it binds specifically to the antigen of interest. The term "derivative" is one that is extensively defined throughout the specification, for example the Examiner is referred to page 35 lines 1-12 of the specification which provides a specific definition for "derivative" as:

> This is a substance which derived from a polypeptide which is encoded by the DNA within a selected rgdp. The derivative polypeptide may differ from the encoded polypeptide by the addition, deletion, substitution or insertion of amino acids, or by the linkage of other molecules to the encoded polypeptide. These changes may be made at the nucleotide or protein level. For example the encoded polypeptide may be a Fab fragment which is then linked to an Fc tail from another source. Alternatively markers such as enzymes, flouresceins etc may be linked to eg Fab, scFv fragments.

In light of this definition and the use of the term at innumerable places throughout the specification, one of skill in the art would find this term to be clear. However, in order to expedite the prosecution, applicants have amended step (ii) in claims 60, 62, 64, 102, 104, 106, and 108 to recite:

> "(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member ***in a functional form comprising a binding domain for its complementary specific binding pair member***, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain thereof encoded by the nucleic acid obtained in step (i)." (***Emphasis added***).

The amendment presented above clarifies that the derivative specific binding pair member produced in step (ii) is one which has a binding domain for its complementary specific binding pair member. Similarly, claims 61, 63, 65, 103, 105, 107, and 109 have been amended to add the following clause:

> "...wherein ***said derivative*** specific binding pair member ***is in a functional form comprising a binding domain for a complementary specific binding pair member***." (***Emphasis added***)

Applicants believe these amendments address all of the Examiner's objections because these amendments provide a functional characteristic for the derivative that is produced by the methods of these dependent claims. The Examiner also queried what is meant by linkage to another molecule. It is correct that the alteration of amino acids might change the binding characteristics of the specific binding pair member. The skilled person will make changes at will for whatever purpose suits him. Nonetheless, the resulting specific binding pair member must still be in functional form and must be about 100 or more amino acids in length. As to "another molecule", this term refers to any other molecule, again at the choice and discretion of the ordinary skilled person. These features are ***method*** features, and a skilled person would

recognize how to carry such steps out. Applicants point the Examiner to claim 20 of related U.S. Patent 5,969,108 in which similar claims were allowed and which demonstrates that the term is in fact clear. Applicants believe that in light of the specification, these claims are imbued with clarity and are in compliance with the requirements of 35 U.S.C. §112, second paragraph. The rejection should be withdrawn and the claims reconsidered for allowance.

IV. Rejections under 35 U.S.C. §102(e) should be withdrawn

The Examiner rejected claim 44, 46, 48-49, 78-81, 86-89 and 94-97 under 35 U.S.C. §102(e) as being anticipated by Dower (U.S. Patent 5,247,908). Applicants respectfully traverse.

Applicants reiterate that the Dower reference as cited, simply does not anticipate any of the claims of the instant invention. The Examiner exhaustively rewrites the rejection previously of record and provides that the instant invention is anticipated because Dower et al. teaches catalytic antibody activities which would read on the enzymes of the instant invention. While Applicants traverse this rejection and incorporate their prior response herein, Applicants have amended Claim 145 to recite "...wherein said enzyme or enzyme fragment is a non-immunoglobulin protein..." Support for this amendment is found throughout the specification for example Example 21 page 151 lines 1 and 2 of the substitute specification where the Applicants refer to ..."non-immunoglobulin proteins, for example enzymes." Catalytic antibodies are immunoglobulin proteins which are explicitly excluded by the claims as amended.

Applicants maintain that Dower fails to disclose an enzyme or a fragment thereof that is at least 100 amino acids and certainly does not provide any teaching or suggestion of an enzyme that is a "non-immunoglobulin protein" as is presently claimed. Applicants reiterate that the only reference in Dower to any protein of a given length is to be found at column 8 lines 45 through 52, where Dower is prophetically discussing the expression of ***V_H domains*** as peptides of up to 120 amino acids. V_H domains are not enzymes or enzyme fragments but rather are by definition immunoglobulin proteins. The Applicants emphasize that the amended claims specifically recite that the enzymes used as parent molecules and which are obtainable by the practice of the present invention are "non-immunoglobulin proteins" as has been taught by the specification from the start

and the failure of Dower to teach such enzymes as is required by the present claims is legally sufficient to require withdrawal of the rejection.

Dower also fails to anticipate the present invention for several additional reasons. For example, Dower provides no disclosure of enzymes of at least 100 amino acids, let alone enzymes of about 200 amino acids (claim 45), or indeed any disclosure of generating specific binding pair members that are enzymes by mutation of a first "parent" enzyme. Contrary to the Examiner's position, an association of VH and VL, by interaction as in a Fab, as described by Dower does not provide a polypeptide of 200 amino acids - it still consists of two polypeptides each of less than 200 amino acids. Regarding the mutation step utilized in the practice of the present invention, the Examiner's suggestion that the cloning techniques to be employed by Dower mean that it teaches "that the nucleic acid sequence would undergo mutation or recombination before it has been inserted into the vectors" lacks factual basis. The Examiner has failed to show how such cloning techniques result in mutations. Further, and contrary to the Examiner's apparent belief, recombination is not mutation. Regardless of these misapprehensions, the applicants reiterate that Dower simply does not teach the mutation of a "first" parent enzyme as is required by the present invention.

The rejections based on the Examiner's characterization of the catalytic antibodies referred to by Dower *et al.* should also be withdrawn, because such antibodies are by definition immunoglobulin proteins while the presently amended claims recite that the enzymes are "non-immunoglobulin proteins."

The Examiner's reference to Dower's mention of enzymes is not germane to the claims of the present invention. Dower refers to cloning such genes from a nucleotide library - i.e. prepare a natural library then look to clone a single protein that binds a ligand you have. Dower states:

> "The protein for which the DNA is enriched and cloned according to the present invention is typically an antibody or fragment thereof, but may also be any protein which may be cloned from a nucleotide library. In addition to antibodies, such proteins may include, for example, growth hormones, interferons, interleukins, hormones, enzymes, zymogens, etc. Proteins which may be cloned

are those for which specific binding partners (e.g. antigen or hapten when the desired protein is an antibody) have been identified."

Nowhere does Dower teach that any such molecules may serve as starting molecules which are then mutated as is required by the present invention nor does it teach molecules over 100 or over 200 amino acids as are required by the present claims.

For the reasons discussed above, the Applicants submit that Dower fails to anticipate the present invention and therefore that the rejections should be withdrawn.

V. Rejections under 35 U.S.C. §103(a) should be withdrawn.

The Examiner reiterated her previous rejection of claims 45-65, 78-109 and 145 under 35 U.S.C.§103, alleging that the claims were obvious in view of the disclosure of Dower. The Examiner maintained her rejection stating that antibodies with catalytic activities could be used as enzymes. While Applicants still traverse the rejection, in order to advance the prosecution of the claims, Applicants have amended the claims such that they specifically state that the enzymes or enzyme fragments are "non-immunoglobulin proteins" which was not in anyway taught or suggested by Dower *et al.*

In summary, Dower fails *inter alia* to teach or suggest a method as presently claimed which includes the mutation of a starting molecule wherein the starting molecule in an enzyme which is a non-immunoglobulin protein, and does not teach or suggest enzymes of at least 100 amino acids. In view of these failures Dower cannot properly render the present invention obvious and therefore the rejection under 35 U.S.C. §103 should be withdrawn.

VI. Conclusion.

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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PD 3/18/03 ~~APPENDIX OF PENDING CLAIMS~~

45. A method according to claim 145 wherein said enzyme or fragment is at least 200 amino acids.

46. A method according to claim 145 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

47. A method according to claim 45 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

48. A method according to claim 145 wherein particles formed by said expression are selected or screened to provide an individual displayed polypeptide specific binding pair member or a mixed population of displayed polypeptide specific binding pair members associated in respective particles with nucleic acid encoding said displayed polypeptide specific binding pair member or specific binding pair members, the specific binding pair member or specific binding pair members thus provided having ability to bind a complementary ligand.

49. A method according to claim 48 wherein the particles are selected by affinity with a complementary ligand.

50. A method according to claim 49 which comprises recovering any particles bound to said complementary ligand by washing with an eluant.

51. A method according to claim 50 wherein the eluant contains a molecule which competes with said particles for binding to said complementary ligand.

52. A method according to claim 49 wherein the particles are applied to said complementary ligand in the presence of a molecule which competes with said particles for binding to said complementary ligand.

53. A method according to claim 48 wherein the particles are selected by enzymatic activity of the displayed polypeptide.

54. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 48; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

55. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 48; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

56. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 49; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

57. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 49; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

58. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 53; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

59. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 53; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

C39 60. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 48, said nucleic acid encoding a polypeptide specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a binding domain for its complementary specific binding pair

member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

61. A method of producing a specific binding pair member, the method comprising:
producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 60, wherein said derivative specific binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

62. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 49, said nucleic acid encoding a polypeptide specific binding pair member or a polypeptide chain component thereof; and
(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a binding domain for its complementary specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

63. A method of producing a specific binding pair member, the method comprising:
producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 62, wherein said derivative specific binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

64. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a selected or screened particle obtained by a method according to claim 53, said nucleic acid encoding a polypeptide specific binding pair member or a polypeptide chain component thereof; and
(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a binding domain for its complementary specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or

by linkage of another molecule, to a polypeptide specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

65. A method of producing a specific binding pair member, the method comprising:
producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 64, wherein said derivative specific binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

78. A method of producing a member of a specific binding pair, the method comprising:
contacting a library of filamentous bacteriophage particles with a desired ligand, wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which bind to said desired ligand.

79. A method according to claim 78 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

80. A method of producing a member of a specific binding pair, the method comprising:
contacting a library of filamentous bacteriophage particles with a desired ligand, wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including said nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which have a desired enzymatic activity.

81. A method according to claim 80 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

82. A method of producing a member of a specific binding pair, the method comprising:

contacting a library of filamentous bacteriophage particles with a desired ligand, wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 200 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which bind to said desired ligand.

83. A method according to claim 82 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

84. A method of producing a member of a specific binding pair, the method comprising:

contacting a library of filamentous bacteriophage particles with a desired ligand, wherein said filamentous bacteriophage particles display on their surface a polypeptide which is a specific binding pair member capable of binding a complementary ligand, and each filamentous bacteriophage particle contains genetic material including nucleic acid encoding said polypeptide, which nucleic acid encoding the polypeptide is provided by mutation of nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof, which said enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 200 amino acids,

wherein said filamentous bacteriophage particles display a population of specific binding pair members, and

separating particles displaying specific binding pair members which have a desired enzymatic activity.

85. A method according to claim 84 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

86. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 78; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

87. A method according to claim 86 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

88. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 80; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

89. A method according to claim 88 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

90. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 82; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

91. A method according to claim 90 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

92. A method of producing a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 84; and

(ii) producing by expression from nucleic acid obtained in step (i) the encoded specific binding pair member.

93. A method according to claim 92 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

94. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 78; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

95. A method according to claim 94 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

96. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 80; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

97. A method according to claim 96 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

98. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 82; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

99. A method according to claim 98 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

100. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 84; and

(ii) producing from nucleic acid obtained in step (i) nucleic acid which encodes a specific binding pair member.

101. A method according to claim 100 wherein said polypeptide is displayed as a fusion with a gene III capsid protein surface component of phage fd or its counterpart in another filamentous phage.

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102. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 78, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and
(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a binding domain for its complementary specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

103. A method of producing a specific binding pair member, the method comprising:
producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 102, wherein said derivative specific binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

104. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 80, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and
(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a bindng domain for its complementary specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

105. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 104, wherein said derivative specific binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

106. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 82, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a binding domain for its complementary specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

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107. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 106, wherein said derivative specific binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

108. A method of producing nucleic acid encoding a specific binding pair member, the method comprising:

(i) obtaining nucleic acid from a separated particle obtained by a method according to claim 84, said nucleic acid encoding a first specific binding pair member or a polypeptide chain component thereof; and

(ii) producing from the nucleic acid obtained in step (i) nucleic acid which encodes a derivative specific binding pair member in a functional form comprising a binding domain for its complementary specific binding pair member, wherein said derivative specific binding pair member is produced by addition, deletion, substitution or insertion of one or more amino acids, or by linkage of another molecule, to said first specific binding pair member or polypeptide chain component thereof encoded by the nucleic acid obtained in step (i).

109. A method of producing a specific binding pair member, the method comprising:

producing said derivative specific binding pair member by expression of nucleic acid produced according to the method of claim 108 wherein said derivative specific

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binding pair member is in a functional form comprising a binding domain for a complementary specific binding pair member.

145. A method of producing a specific binding pair member, which method comprises:

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expressing in recombinant host cells a library of nucleic acid sequences encoding a genetically diverse population of polypeptides, which library of nucleic acid sequences is provided by mutating nucleic acid encoding a specific binding pair member which comprises an enzyme or fragment thereof wherein said enzyme or fragment thereof is a non-immunoglobulin protein, which enzyme or fragment thereof is able to bind a ligand of said enzyme and is at least 100 amino acids,

wherein said polypeptides encoded by the library are displayed at the surface of filamentous bacteriophage particles, and wherein genetic material of each filamentous bacteriophage particle displaying a polypeptide includes nucleic acid